EXHIBIT 6

CONSUMPTION OF OMEGA-3 FATTY ACIDS MAY REDUCE THE RISK OF CORONARY HEART DISEASE – A REVIEW

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INTRODUCTION

Cardiovascular disease is reported as the leading cause of death in the United States. About 30 million Americans suffer from heart or blood vessel disease and as many as 27 million from high blood pressure. In 1991, 765,000 people died of heart disease and 190,000 died of stroke and other vascular complications--a total of 400 deaths per 100,000 people--and the number of deaths has increased since then. Cardiovascular disease accounts for 45 percent of all deaths in the United States. A quarter of the people who have a heart attack die within three hours of the first symptoms. Many experience sudden unexpected death and do not even reach a hospital. Another 25 percent die within the first few weeks after a heart attack. Cardiovascular disease is reported to cost the United States $65 billion annually; more than $38 billion of this cost is related to premature death (i.e., death before the age of 65).

Some dietary factors play a major role in determining the blood level of cholesterol, various lipoproteins, and triglycerides, which are considered major risk factors for cardiovascular disease. Some foods and individual nutrients appear to have a protective role in cardiovascular disease as well as in cancer.

The fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 fatty acids found in most cold-water fish, such as tuna, salmon and mackerel, fish oils such as unhydrogenated menhaden oil, and fish liver oils such as cod liver oil. The adequate consumption of this class of fatty acids normalizes the levels of blood lipids such as triglycerides, reduces the tendency for blood-clot formation, and stabilizes the heartbeat against potentially fatal arrhythmias, especially under conditions of inadequate coronary blood flow, such as during a heart attack. Fish oil rich in omega-3 fatty acids is recognized as having cardioprotective actions.

The fatty acid alpha-linolenic acid (ALA) is an omega-3 fatty acid found in a few commonly available unprocessed oils, especially flax seed oil, canola oil, soybean oil, and walnut oil and in other oils such as perilla oil. Refining such as deodorization and partial hydrogenation causes loss of the omega-3 fatty acid ALA, which can range from a minor loss to near total loss. When levels of this omega-3 fatty acid in the diet are not swamped by high levels

of the fatty acid linoleic acid (LA), an omega-6 fatty acid, i.e., the ratio of LA/ALA is not greater than 3.0, there is some conversion in the human from ALA to EPA and DHA, affording the body some accumulation of EPA and DHA in the phospholipids of circulating platelets and the protection it offers against platelet aggregation. Without adequate EPA and DHA in phospholipids, the modulating role of the derivative prostaglandins are not seen.

Omega-3 fatty acids are precursors to eicosanoids, e.g., prostaglandins and leukotrienes. These eicosanoids modulate metabolic actions in many tissues by their effects on, e.g., tissue hormones and prehormones, signal molecules, and receptors. They are responsible for maintenance of a desirable balance of, e.g., endogenous vasoconstriction, activity of the renin-angiotensin system, salt and water balance, peripheral sympathetic tone, cardiac output and baroreceptor settings, all functions in the body that are of critical importance to proper maintenance of a healthy cardiovascular system.

Adequate consumption of omega-3 fatty acids may reduce the risk of coronary heart disease through a number of effects on cardiovascular risk factors, especially related to reduction of triglycerides, improvement of heart rate variability, and risk of fatal arrhythmias. Support for this statement may be found in the following review and evaluation of recent scientific literature, which includes a discussion of:

a) the competence and reliability of recent (1994-present) science supporting the claim;

b) the level of intake required to achieve beneficial results and anticipated levels of omega-3 fatty acid consumption by use of a supplement compared to the probable level needed when the nutrient may be consumed in a well-balanced diet;

c) the safety of the nutrient at dose levels and consumption levels needed to produce the physiologic effect.

EVALUATION OF CURRENT SCIENTIFIC LITERATURE WITH RESPECT TO THE EFFECT OF OMEGA-3 FATTY ACIDS ON CORONARY HEART DISEASE RISK FACTORS

In order to determine the extent to which the current scientific literature supports the claim that "consumption of omega-3 fatty acids may reduce the risk of coronary heart disease," 168 published articles were identified from Medline for the years 1994 to 1999 as relevant to the topic.

Of the 168 articles, 74 were reports of clinical treatments and clinical trials (44%), 16 were reports of epidemiological studies (9.5%), 36 were review/tutorial articles (21.4%), 28 were reports of basic research in animal and/or cell culture models (16.7%), 5 were letters to the editors (3%), 5 were articles in medical news letters (3%), and 4 were editorials (2.4%).

CONSUMPTION OF OMEGA-3 FATTY ACIDS
Mary G. Enig, Ph.D. 11/15/99

Of the reports identified by Medline as clinical treatments and clinical trials, 12 were published in 1999 (through September), 12 were published in 1998, 13 were published in 1997, 13 were published in 1996, and 12 were published in 1995. On examination several reports listed by Medline as clinical trials turned out to actually be review articles where the author included summary reports of clinical trials. In each case, the original publications from the trials were consulted for verification of the information.

CLINICAL TREATMENT AND CLINICAL TRIALS LITERATURE

Review of selected representative literature

Investigators of the **GISSI-Prevenzione trial (1999)** concluded that treatment with 1 gram per day of n-3 PUFA in the form of ethyl esters of eicosapentaenoic acid and docosahexaenoic acid (850-882 mg) "led to a clinically important and statistically significant benefit" of lowered the risk of the primary endpoint of a fatal cardiovascular event. This trial was reviewed for the Cardiovascular News Meeting Highlights of the 48th Scientific Sessions of the American College of Cardiology under the section on Preventive Cardiology by Ferguson (1999). The summary stated: "In patients with a recent history of MI, dietary supplementation with n-3 PUFA (1 g/day)...seems to significantly reduce long-term cardiac events, total mortality, and sudden cardiovascular death."

In this review, which Medline lists as a clinical trial publication, **Harris (1999)** gives an overview of the history of lipid-altering effects of the n-3 PUFA, an evaluation of low dose studies, a brief review of animal studies, and reports on two clinical intervention studies with n-3 PUFA and coronary heart disease, which were both prospective, randomized trials with hard endpoints, i.e., cardiac events, and mortality. The first trial, reported in 1989 (Harris' reference 8) was called DART, and used an intake of oily fish for the experimental group, which provided about 200 to 400 grams of fish a week and approximately 500 to 700 mg/day of eicosapentaenoic acid and docosahexaenoic acid. In the ensuing 2 years, those on the fish diet had 29% fewer deaths. The second trial is Singh et al (1997), known as the Indian Experiment. In this trial, approximately 360 patients who presented with myocardial infarction were randomized to 2 g of n-3 PUFA (6 capsules of Maxepa), 2.9 g of alpha-linolenic acid (20 g of mustard seed oil), or placebo. The patients were followed for 12 months with a significant reduction in new cardiac events. Harris concludes in summary that "there is extensive and consistent documentation of the ability of marine n-3 [PU]FA to reduce serum triglycerides levels in humans by 20-30% at doses of 3-4 g per day." Harris had previously reviewed several earlier studies of the impact of fish oil omega-3 on hypertriglyceridemia (see reviews section below, Harris 1996).

Based on an evaluation of 82 male children from age 7-14 years, who were divided into groups with and without risk factors of cardiovascular pathology **Kozycheva and Slezka (1998)** report a "correcting effect" by dietary omega-3 PUFA from marine sources on the composition of "erythrocyte fatty acid defects" at early stages of disease. This was especially observed in the case of children who had myocardial infarction heredity. The authors conclude that dietary

omega-3 PUFA can be used for preventative treatment of children with cardiovascular disease heredity.

Pogozheva et al (1998) conducted a clinical trial to study levels of natural antibodies against catecholamines in 138 patients with cardiovascular diseases. A comparative analysis of the influence of "antiatherosclerotic" diets with omega-3 PUFA from both plant and animal sources was made. The greatest "immunocorrection effect" was found when the diet was enriched with omega-3 PUFA freshwater fish fat.

Heart rate variability and omega-3 PUFA

Decreased heart rate variability (HRV) is associated with increased coronary mortality due to sudden cardiac death **(Christensen JH et al 1999a)**, and in fact, HRV is considered "a powerful predictor of mortality and of arrythmic events in humans.". Findings from a number of clinical trials from several research facilities published between 1996 and 1999 reported on the beneficial effect between dietary intake of omega-3 polyunsaturated fatty acids and HRV. These research reports include: Christensen JH et al 1999a, Christensen JH et al 1999b, Christensen JH et al 1999c, Christensen JH et al 1998, Christensen JH et al 1997a, Christensen JH et al 1997b. A representative sample of these trials are reviewed.

Because there was evidence for an anti-arrhythmic effect of n-3 polyunsaturated fatty acids (n-3 PUFA) in animals, Danish researchers decided to evaluate a possible beneficial anti-arrhythmic effect of consumption of the long-chained n-3 PUFA on heart rate variability. Several studies were undertaken (Christensen JH et al 1999a). Three different groups of people were evaluated in these studies, and they included 1) patients with previous myocardial infarction (Christensen et al 1999a, 1997, 1996), 2) patients with chronic renal failure (Christensen JH et al 1998), and 3) healthy volunteers (Christensen JH et al 1999a). Additionally, Christensen JH et al (1999c) had validated the measures of HRV and risk for sudden cardiac death. The authors' conclusion was that "the results showed a beneficial effect of n-3 PUFA on HRV in...[these]...populations...[and that their]...data may explain the findings from other studies, namely that a low occurrence of sudden cardiac death is observed in subjects with and without coronary heart disease who regularly eat fish."

Leaf et al (1999) have reviewed the recent studies which they report identifies what is likely the major mechanism by which n-3 PUFA exerts its antiarrhythmic effect. They report that PUFA stabilize the electrical activity of isolated cardiac myocytes by inhibiting sarcolemmal ion channels; this then requires a stronger electrical stimulus to elicit an action potential resulting in a markedly prolonged refractory period.

An intervention trial was assessed in 52 patients with a history of previous myocardial infarction and left ventricular dysfunction. The content of n-3 PUFA in platelets was monitored and was found to be closely associated with the patient's fish-consuming habits. This study reported that a significant positive correlation was observed between the n-3 fatty acid docosahexaenoic acid and heart rate variability **(Christensen et al 1997a)**.

The post-MI patients in the above study were randomly evaluated in the next study, which investigated the effect of supplementing dietary n-3 PUFA on ventricular arrhythmias and heart rate variability (HRV) in patients with a previous myocardial infarction. In a double-blind, placebo-controlled study, patients were given 5.2 g per day of n-3 PUFA or placebo and HRV response was measured from a 24 hour Holter recording both at baseline and, following supplementation, at the end of 12 weeks. The study showed significantly increased HRV after n-3 PUFA compared to both baseline values ($p = 0.04$) and to controls ($p = 0.01$). This was interpreted as supporting the hypothesis that n-3 PUFA may have an anti-arrhythmic effect in humans (Christensen et al 1997b)

In a clinical trial published in the *American Journal of Clinical Nutrition*, **Christensen JH et al (1999a)** studied the dietary intake of capsules containing 6.6 g or 2.0 g per day of long-chain n-3 polyunsaturated fatty acids (PUFA) reesterified from fish oil. Function was determined by a 24 hour Holter recording in healthy volunteers; this double-blind study included both males and females. The researchers' conclusion was that the "...study showed a beneficial effect of n-3 PUFA on HRV in healthy men, suggesting an antiarrhythmic effect of n-3 PUFA." The effect was not seen in the women.

Li et al (1999), evaluated thrombotic risk factors in vegetarian men who are known to have higher platelet aggregability than omnivores. The authors concluded that, in this study where the normal vegetarian diet was supplemented with added sources of ALA from vegetable oils such as canola and linseed, there was a significant increase in EPA and DHA as well as an increase in the ratio of n-3 to n-6 PUFAs in platelet phospholipids and plasma lipids in these subjects.

Singh et al (1997) (as reviewed below) compared the effects of both fish oils supplements and mustard oil in patients with suspected acute myocardial infarction. In this randomized, placebo-controlled trial, the effects of treatment with fish oil (eicosapentaenoic acid, 1.08 g/day) and mustard oil (alpha-linolenic acid, 2.9 g/day) were compared for 1 year. There were 122 patients treated with fish oil (group A), 120 patients treated with mustard oil (group B), and 118 patients treated with placebo (group C) all with suspected acute myocardial infarction (AMI). Treatments were started on average approximately 18 hours after the symptoms of AMI brought them in for treatment in all three groups. The extent of cardiac disease, rise in cardiac enzymes, and lipid peroxides were comparable among the groups at entry into the study. After 1 year total cardiac events were significantly less in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% vs. 34.7%, $p < 0.01$). Nonfatal infarctions were also significantly less in the fish oil and mustard oil groups compared with the placebo group (13.0% and 15.0% vs. 25.4%, $p < 0.05$). There was no significant reduction of total cardiac deaths in the mustard oil group but the fish oil group had significantly less cardiac deaths compared with the placebo group (11.4% vs. 22.0%, $p < 0.05$).

In a multicenter study, **Archer et al (1998)** have evaluated dietary intake of omega-3 fatty acids related to hemostatic factors which are known to play an important role in the complications of ischemic heart and vessel disease. Dietary fats such as omega-3 PUFA have

been shown to possibly influence hemostatic factors. It was noted that most studies reporting an inverse association between cardiovascular disease and fish and n-3 fatty acid consumption have used supplemental doses of fish oil or intakes exceeding the typical amount consumed by the U.S. population. This report examined the associations of usual intakes of fish, linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid with fibrinogen, factor VII, factor VIII, and von Willebrand factor in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. The analyses were reported for 1672 black and white men and women aged 24 to 42 years in 1992 to 1993. After adjustment for age, body mass index, diabetes, number of cigarettes smoked per day, race, and energy and alcohol consumption, no significant associations were observed between those who consumed no fish versus those who consumed the highest level of dietary fish with respect to fibrinogen, factor VIII, or von Willebrand factor for any race-sex group. Comparisons of tertile 1 versus tertile 3 for dietary linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid were also not significantly associated with fibrinogen, factor VII, factor VIII, or von Willebrand factor for any race-sex group. These data were interpreted to suggest that customary intakes of fish and n-3 fatty acids in populations that generally do not consume large amounts of these food items are not associated with these hemostatic factors.

EPIDEMIOLOGICAL LITERATURE

Guallar et al (1999) studied the levels of omega-3 fatty acids in adipose tissue related to risk of myocardial infarction as part of the EURAMIC study. They found a slight protective effect of alpha-linolenic acid and no protective effect of docosahexaenoic acid and did not identify any eicosapentaenoic acid content.. Since, there are usually no elongated omega-3 fatty acids (omega-3 PUFA) stored in adipose, because they are basically membrane fatty acids, it is unlikely that the findings in this study have much meaning regarding the relationship between omega-3 PUFA and risk of myocardial infarction.

Kaminskas et al (1999) compared abdominal adipose fatty acids from two populations with different cardiovascular risk. Lithuanian men, who have four times higher coronary heart disease mortality than Swedish men, in spite of having lower total and LDL cholesterol, were found to have significantly higher percentage of long-chain PUFA and lower percentage of saturated fatty acids, especially myristic acid. Since the PUFA normally would be found in membrane tissue where they provide precursor to eicosanoids, and the saturates would normally be found in the adipose, it could be that the findings in this study may be indicative of some lipid abnormality unrelated to the long-chain PUFA specifically.

Hu et al (1999) evaluated the risk of fatal ischemic heart disease (IHD) among women as it was related to their dietary intake of alpha-linolenic acid. This prospective cohort study with ten years of follow-up was reported to support the hypothesis that a higher intake of alpha-linolenic acid is protective against fatal ischemic heart disease (IHD). Higher consumption of foods such as oil-based salad dressing that provide polyunsaturated fats, including alpha-linolenic acid, may play a role in the reduction of the risk of fatal IHD.

Aschereio et al (1996) examined the association between fat intake and the incidence of coronary heart disease in a cohort of men of middle age and older as part of the health professionals follow up study in the United States. The data did not support the strong association between intake of saturated fat and risk of coronary heart disease suggested by international comparisons, but it did support a specific preventive effect of linolenic acid intake.

REVIEWS

Roche and Gibney (1999) have reviewed studies which used both short- and long-term supplementation of omega-3 fatty acids in amounts ranging from 1 g per day to 28 g per day from fish oils. After evaluating the studies which showed lowering of both fasting and postprandial triglycerides, these researchers concluded that although "the precise biochemical nature of this effect remains to be established...reduction of postprandial plasma TG concentrations by n-3 PUFA may partly explain why n-3 PUFA intake is inversely related to CHD mortality.

Schmidt and Dyerberg (1999) have reviewed a number of trials and have concluded that a 1989 study provided "clinical evidence for a protective role of n-3 PUFA in CHD." They also note that the research (Christensen 1996) on heart rate variability showed a benefit from n-3 PUFA. However, in this review, the authors still call for increased trials for both fish and fish oil concentrates. They note that many populations do not have fish intake that would provide 1 g/week of n-3 PUFA, and that, additionally, "some people dislike seafood."

Connor and Connor (1997) ask the question "Are fish oils beneficial in the prevention and treatment of coronary artery disease?" Their answer is that the "n-3 fatty acids of fish and fish oil have great potential for the prevention and treatment of patients with coronary artery disease." They report that unlike many of the pharmaceutical agents used to treat coronary artery disease that have just a single mechanism of action, the omega-3 PUFA of fish oil have "multifaceted actions." As noted by other researchers, one of the most important effects of the omega-3 PUFA is the prevention of arrhythmias. The documentation for this effect has been derived from experiments in cultured myocytes, experiments in animals, epidemiologic correlations, and clinical trials. The Connors note that the ability of these omega-3 PUFA to inhibit ventricular fibrillation and consequent cardiac arrest is especially important. They discuss several mechanism including the several antithrombotic actions of EPA, particularly in inhibiting the synthesis of thromboxane A2, the prostaglandin that causes platelet aggregation and vasoconstriction. Further they report that fish oil retards the growth of the atherosclerotic plaque by inhibiting both cellular growth factors and the migration of monocytes. Also, omega-3 PUFA is reported to promote the beneficial synthesis of nitric oxide in the endothelium. In experiments in humans, a profound hypolipidemic effect of fish oil, is seen, especially with regard to lowering of plasma triacylglycerol, and inhibition of very-low-density lipoprotein production and apolipoprotein B synthesis. Fish oil is also said to have a mild blood pressure-lowering effect in both normal and mildly hypertensive individuals. The Connors state in their abstract that "these composite effects suggest a prominent therapeutic role for fish oil in the prevention and treatment of coronary artery disease."

Harris (1996, 1999) has reviewed several studies of the impact of fish oil omega-3 on hypertriglyceridemia. He notes that triglyceride lowering is the most consistent effect of dietary fish oils, having been observed in Greenland Eskimos and subsequently in controlled clinical trials. In those early studies, total cholesterol levels are not altered, but there was a transient rise in LDL levels, especially in hypertriglyceridemic patients. In later studies which followed large numbers of patients from 6-9 months there was a persistence of the hypotriglyceridemic effect as long as the fish oil treatment continued, and these was evidence from the studies that the LDL raising effect may not persist. Further, Harris notes the safety of fish oils was also supported in the studies because problems with excessive bleeding and worsening glycemic control did not materialize. However, in one of the studies, dietary fish oil was reported to be ineffective in slowing the rate of restenosis after coronary angioplasty.

De Deckere et al (1998) reports on conclusions from an expert workshop which reviewed the health effects of n-3 polyunsaturated fatty acids (PUFA). Among their conclusions were that 1) consumption of fish may reduce the risk of coronary heart disease (CHD) and that people at risk for CHD are therefore advised to eat fish once a week. They noted that the n-3 PUFA in fish are probably the active agents in this effect. Therefore, people who do not eat fish should consider obtaining 200 mg of very long chain n-3 PUFA daily from other sources. They also felt there is incomplete but growing evidence that consumption of the plant n-3 PUFA, alpha-linolenic acid, reduces the risk of CHD andd that an intake of 2 g/d or 1% of energy of alpha-linolenic acid appears prudent. They further noted that the ratio of total n-3 over n-6 PUFA (linoleic acid) is not useful for characterizing foods or diets because plant and marine n-3 PUFA show different effects, and because a decrease in n-6 PUFA intake does not produce the same effects as an increase in n-3 PUFA intake. Separate recommendations for alpha-linolenic acid, marine n-3 PUFA and linoleic acid were preferred.

ANIMAL AND CELL CULTURE STUDIES

An animal study by **Nair et all (1999)** found a response in the pig model that suggested a "possible role of nonesterified (n-3) polyunsaturated fatty acids in the prevention of arrhythmias."

Hishinuma T et al (1999) studied the effect of omega-3 PUFA on changes of lipid profiles and prostacyclin production by cultured bovine aortic endothelial cells. They report that their findings "suggest that EPA, docosapentaenoic acid, and DHA are interconverted to each other, and anti-aggregatory effects of EPA or DHA may be partially due to the stimulation of prostacyclin formation in endothelial cells."

Animal studies have confirmed the protective effect against ischemia-induced fatal arrhythmias (**Billman et al 1999**).

Hartman (1995) has reviewed the results of a 5-year study of survivors of a first myocardial infarction, which reports the prevention of secondary coronary events as an effect of

an alpha-linolenic acid-enriched diet (experimental) compared with the prudent diet of the American Heart Association (control). The data were from the dietary intervention study of de Lorgeril et al (1994). During an average of 27 months of follow-up, there were 5 nonfatal myocardial infarctions and 3 cardiac deaths in the experimental group versus 17 nonfatal myocardial infarctions and 16 cardiac deaths in the control group. The overall mortality was 20 in the control group and 8 in the experimental group. The interpretation of this study was that a diet enriched with alpha-linolenic acid appears to be effective in secondary prevention of coronary events, but the actual trial had three dietary components being used concurrently; in addition to the increased ALA component, the second component was increased consumption of fish, and the third component was that it was to be a "Mediterranean" diet.

Mantzioris et al 1995 reports that increased concentrations of cellular eicosapentaenoic acid (EPA) have been shown to be beneficial in coronary heart disease, hypertension, and inflammatory disorders. Successful long-term strategies for increasing cellular EPA concentrations require an understanding of the relationships between cellular concentrations of EPA and dietary amounts of ALA, a precursor of EPA, and dietary amounts of linoleic acid (LA), which can act as an antagonist of ALA conversion to EPA (and DHA). With this dietary intervention trial, which studied healthy human volunteers and which incorporated ALA-rich vegetable oil (flaxseed oil) against a background diet low in LA, the researchers were able to examine these relationships. Linear relationships were reported between dietary ALA and EPA in plasma fractions and in cellular phospholipids. By contrast there was no relationship observed between dietary LA and tissue concentrations of its metabolite, arachidonic acid (AA). There was an inverse relationship between dietary ALA and DHA concentrations in the phospholipids of plasma, neutrophils, mononuclear cells, and platelets. The results of this study indicated that increasing dietary ALA would elevate tissue EPA concentrations in a predictable manner. It was concluded that this insight could facilitate the rational planning of practical dietary strategies for the long-term elevation of EPA concentrations in tissues.

Santos et al 1995 studied the effects of dietary supplementation with fish on plasma fatty acid levels in 20 coronary heart disease patients who had suffered acute myocardial infarction. The study was divided into three periods which included the term of hospital admission, after 8 weeks on a special diet designed for patients with ischemic heart disease, and after 4 weeks on an n-3 PUFA-supplemented diet in which red meat was replaced with lean and fatty fish. At the end of each period, the subjects were given a 48-hour recall dietary questionnaire, to assess compliance with the diet, and blood samples were collected for the determination of plasma fatty acids. Stearic acid was significantly decreased after the fish diet, but fatty acids such as palmitoleic and oleic acid showed no significant changes throughout the study. At the end of the 4-week period when the fish diet was consumed there was a significant decrease in linolenic acid and the significant increase in its long-chain derivatives EPA and DHA in the plasma fatty acids, which was thought to show beneficial effects on coronary heart disease.

Horrocks and Yeo (1999) have reviewed the epidemiological studies which have shown a strong correlation between fish consumption and reduction in sudden death from myocardial infarction and the reduction is approximately 50% with 200 mg a day of DHA from fish.

DHA is considered the active component in fish. They note that not only does fish oil reduce triglycerides in the blood and decrease thrombosis, but it also prevents cardiac arrhythmias. They also suggest that the association of DHA deficiency with depression is the reason for the robust positive correlation between depression and myocardial infarction. Patients with cardiovascular disease are often advised to adopt a low-fat diet with a high proportion of carbohydrate, as are patients with Type II diabetes . However, a study with women showed that this type of diet increased plasma triglycerides and the severity of Type II diabetes and coronary heart disease. Both DHA and EPA are present in fatty fish (salmon, tuna, mackerel). DHA is also present at low levels in meat and eggs. The shorter chain n-3 fatty acid, ALA, noted not to be converted very well to DHA in man.

CONVERSION OF ALA TO EPA AND DHA IN HUMANS

There was previously thought to be substantial conversion of the omega-3 fatty acid alpha-linolenic acid (ALA) to the elongated omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found most commonly in fish and fish oils. In fact, Bordoni et al (1996) had reported a 90% conversion of ALA to elongated forms of n-3 PUFA. Research reported in 1998 (**Gerster**), which measured the conversion of ALA labeled with radioisotopes, has shown that the conversion in adult humans is only approximately 6% to EPA and 3.8% to DHA when the background diet is high in saturated fat, but the conversion is reduced 40 to 50% when the diet is rich in omega-6 PUFA. Since the typical diet in the United States is high in omega-6 PUFA, the levels of EPA and DHA that can be obtained from ALA-rich vegetable oils through conversion in humans is not particularly high and are probably on the order of 3% conversion to EPA and less than 2% to DHA. In addition, most of the vegetable oils that have ALA only in their unprocessed form have had the biologically available ALA totally removed by partial hydrogenation or changed to a form that is not biologically available by refining such as deodorization and/or decolorization.

Suzuki et al (1997) measured the uptake into brain tissues of omega-3 fatty acids from different sources and provided an example of the extent to which ALA may be bioavailable. The percentage of DHA found in the brain was ranked in the following order: the salmon oil diet group > the sardine oil diet group > > the perilla oil diet group > > the lard and palm oil diet groups for the 30 day feeding trial. When the animals were fed purified fatty acids, the uptake was in the order of the DHA diet group > > the eicosapentaenoic acid and alpha-linolenic acid diet groups for the 6 day feeding trial.

IN SUMMARY:

THE KNOWN EFFECTS OF OMEGA-3 PUFA ON CORONARY HEART DISEASE

From a review of the current scientific literature one can see that some of the mechanisms have been identified whereby omega-3 PUFA from fish oil can be said to have beneficial physiological and biochemical effects, which result in the prevention of coronary heart disease. At least three such mechanisms, i.e. triglyceride lowering, the raising of heart rate variability,

and reduction of fatal arrhythmias have been well studied. In the studies reviewed, the adequate dietary intake of omega-3 PUFA, was primarily from whole fish oils.

In conclusion, it is reported in peer reviewed scientific literature that the dietary intake of adequate amounts of omega-3 PUFA has been shown to 1) decrease adversely high levels of triglycerides (TG) and very low density lipoproteins (VLDL), thus decreasing the risk of coronary heart disease; 2) increase heart rate variability and thereby decrease the risk of sudden death from heart attack thus helping to prevent a first heart attack; and 3) help prevent second heart attack in individuals who have sustained a first heart attack.

REGARDING LEVELS OF OMEGA-3 PUFA THOUGHT TO BE BENEFICIAL

The levels of omega-3 PUFA in the daily diet needed to maintain optimal omega-3 PUFA in the tissues and to provide physiologically and biochemically beneficial effects are approximately 3 to 4 g/day of fish oil omega-3, but some studies have reported benefits at 1 g/day omega-3 PUFA.

Levels of fish required to achieve the 3-4 g/day are much higher than the levels typically consumed in the United States. Not all fish have sufficiently high levels of fat to provide even 1 g/day in a typical 100 g serving.

Plant omega-3 (ALA) is variably converted to omega-3 PUFA depending on background diet of the individual; a background diet high in saturated fat is needed for optimal conversion and a diet high in omega-6 linoleic acid (LA) decreases conversion by about 50%. In the United States and Canada and other parts of the world this high saturated fat diet is discouraged and usually replaced with a diet high in omega-6 LA.

REPORTED LEVELS OF OMEGA-3 PUFA FROM FISH OILS AND OMEGA-3 ALPHA-LINOLENIC ACID FROM VEGETABLE OILS FED TO HUMANS

GISSI clinical trial (1999): 1g/d omega-3 PUFA long term containing 850-882 mg EPA and DHA as ethyl esters.

Roche and Gibney (1999) reviewed studies which used both short- and long-term supplementation ranging from 1 g/d omega-3 PUFA (Roche and Gibney 1996) to 28 g/d omega-3 PUFA (Harris et al 1988)

Harris (1999) reviewed "low-dose" 3-4 g/d omega-3 PUFA on average, and other studies "up to 25 g/d omega-3 PUFA

Tinker et al (1999) fed 13.2 g fish oil which contained 5.2 g omega-3 PUFA in a clinical study which reported significant effects on lowering postprandial triglyceride and lipoprotein levels.

CONSUMPTION OF OMEGA-3 FATTY ACIDS
Mary G. Enig, Ph.D. 11/15/99

von Schacky et al (1999) fed 3 g/day of fish oil which contained 1.5 g omega-3 PUFA for 21 months after an initial 3 months of 6 g/day of fish oil. They reported modest effects on coronary atherosclerosis with fish oil treated patients having fewer cardiovascular events.

Nordoy et al (1998) fed 4 g/day of purified omega-3 PUFA in conjunction with Simvastatin to patients with combined hyperlipidemia. They report that the combined treatment had a beneficial additive effect.

Sirtori et al (1997) fed (2.58 g x 3) 7.74 g/d of EPA and DHA as ethyl ester for 2 months and then (1.72 g x 2) 3.44 g/d of EPA and DHA as ethyl ester for an additional 4 months.

LEVELS OF OMEGA-3 PUFA IN FISH

According to **Connor and Connor (1997)** (Table 2 in *AJCN*), fish having less than 0.5 g omega-3 PUFA/100 g edible portion are carp, catfish, Atlantic cod, Pacific cod, flounder, haddock, halibut, ocean perch, walleye pike, red snapper, sole sturgeon, swordfish, brook trout, all crustaceans, New Zealand abalone, clam, octopus, scallop, squid. Fish having 0.5 to 1 g omega-3 PUFA/100 g edible portion are striped bass, Florida pompano, shark, rainbow trout, tuna, blue mussel, Pacific oyster. Fish having 1 to 1½ g omega-3 PUFA/100 g edible portion are European anchovy, carp, mullet, sablefish, all salmon. Fish having 1.5 to 2 g omega-3 PUFA/100 g edible portion are Atlantic herring, Pacific herring, lake trout. Fish having greater than 2 g omega-3 PUFA/100 g edible portion are Atlantic mackerel (2.5) and sardines in sardine oil (3.3).

Although codfish is high in omega-3 PUFA, i.e., 42.86% for the Atlantic variety and 33.33% for the Pacific variety, the levels of total fat are so low that more than 300 g /day of Atlantic codfish or more than 500 g/day of Pacific codfish would be needed to provide 1 g/day of omega-3 PUFA.

Flounder is a very popular fish in the U.S. It has 1 g of fat and 0.2 g of omega-3 PUFA per 100 g of fish. Therefore 500 g of this fish would be needed to provide 1 g of omega-PUFA. Haddock and halibut are also popular fish which are low in fat and thus require large amounts to provide 1 g/day of omega-3 PUFA. For haddock the amount of fish would be 500 g/day and for halibut the amount of fish would be 250 g/day.

For fish such as herring, 62.5 g/day of the Atlantic variety would provide 1 g/day of omega-3 PUFA; for the Pacific variety 59 g/day would suffice. Because mackerel is relatively high in fat with moderate levels of omega-3 PUFA, 40 g/day of this fish would provide 1 g/day of omega-3 PUFA and 100 g/day of the fish would provide 2.5 g/day of omega-3 PUFA. Mackerel is not a very popular fish in the U.S. Sardines packed in sardine oil provide 3.3 g omega-3 PUFA for 100 g, but the drained content of a 92 g can would provide 1.36 g omega-3 PUFA.

REGARDING SEPARATED FISH OIL IN CAPSULES

CONSUMPTION OF OMEGA-3 FATTY ACIDS
Mary G. Enig, Ph.D. 11/15/99

Omega-3 PUFA is most commonly available (usually in capsule form) from fish liver oil (cod and shark), herring oil, menhaden oil, salmon oil, and tuna oil. Capsules are usually 1 gram in size. The amounts of EP and DHA vary depending on fish source, since these fish oils do not have identical fatty acid compositions, and also vary depending on any processing, e.g., distillation to concentrate individual fatty acids.

REGARDING REPORTS OF TOXIC LEVELS IN HUMANS

Connor & Connor (1997) recommend up to 15 g/day fish oil. Connor and colleagues fed 50 g fish oil in a 3000 kcal diet with no report of toxicity.

EXAMPLE OF RECOMMENDATIONS FROM SCIENTIFIC LITERATURE

Connor & Connor (1997) recommend dietary intake of omega-3 PUFA from fish and fish oil to prevent coronary disease in highly susceptible people and to treat patients with established coronary heart disease since the omega- PUFA "...greatly inhibit the atherosclerotic process and coronary thrombosis by many actions..."

RECOMMENDED LEVELS OF SEPARATED FISH OIL AS SUPPLEMENT

Connor & Connor (1997) recommend that fish oils be used in addition to consumption of fish at a dose range between 6 and 15 g/day if intensive treatment of various forms of hyperlipidemia as well as the production of an antithrombotic state is desired. Further for individuals who are unable to consume fish or shellfish, they advise the use of fish oil for primary prevention at levels of 2-3 g/d with the higher doses being used for secondary prevention and "the attainment of discrete endpoints of plasma lipid and lipoprotein concentrations and platelet function."

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